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The Binding of *Helix pomatia* and *Ulex europeus* Agglutinins to Normal and Psoriatic Skin

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We have compared the staining patterns of *Ulex europeus* agglutinin (UEA) I-FITC and *Helix pomatia* agglutinin (HPA)-FITC on normal and psoriatic epidermis in order to follow the production of the binding sites as a function of maturation. We have further characterized them with respect to solvent extraction and enzyme digestion. The bandlike pattern of membrane staining by UEA I in the upper spinous and granular layer cells of normal epidermis is lost in psoriasis. Instead there is a fainter cytoplasmic staining which is largely sensitive to chloroform/methanol extraction, and thus presumably is glycolipid in nature. Epidermal binding of HPA to normal skin sections is mainly seen in cell membranes. It spares the basal layer and then increases from the suprabasal region to the granular layer. HPA staining in the spinous layer is destroyed by extraction with Triton X-100. In contrast, binding to the membranes of cells in psoriatic epidermis is triton-resistant. The result indicates the production of a component early in the maturation pathway which has no counterpart in normal skin. HPA binding to the spinous cells of symptomless skin from psoriatic patients shows decreased sensitivity to Triton X-100 by comparison with normal. The results are discussed in terms of changes in the pathway of keratinocyte maturation in psoriasis.

Lectins have been widely used to follow changes in the patterns of carbohydrate side chains of glycoconjugates on cells during differentiation [1–3] and malignancy [4–6]. Different lectins, possessing a variety of sugar specificities, show characteristic patterns of staining in epidermis [7–9] which have been related to the development of an increasingly complex series of glycoconjugates during keratinocyte maturation [2]. In general, the basal layer binds comparatively few lectins such as concanavalin A, *Phaseolus hepaticus*, and wheat germ agglutinins and even in these cases binds them to a lesser extent than does the malpighian layer [9,10]. A number of lectins such as those from peanut, soybean, *Saphora japonica*, and *Helix pomatia*, bind to the malpighian layer in a manner which increases in the spinous layer toward the stratum granulosum [7,8,11]. *Ulex europeus* (UEA) I shows the narrowest range of binding, staining only the most superficial layers of the stratum corneum [7,8,10,12].

A number of studies have reported abnormalities in the glycocalyx of epidermal cells in psoriasis [13–15]. With the availability of lectins, it has become possible to characterize changes in glycoconjugates more precisely. Experiments on the binding of lectins to isolated cells have shown alterations in the affinities and numbers of reactive sites, notably in the cases of UEA I [16,17]. In addition, fucose-containing glycoproteins, which include the UEA I binding site [18–22], show considerable changes in structure and peptide chemistry. In such studies, however, it is difficult to relate the changes to the maturation of the keratinocytes, but this can be done in epidermal sections, using the architecture of the tissue to follow the appearance of glycoconjugates. Accordingly, we have compared the distribution of lectin binding sites in normal and psoriatic epidermis by means of fluorescence microscopy of frozen sections.

Of the lectins we have studied, we have concentrated in this paper on UEA I and *Helix pomatia* (HPA) which are two lectins whose binding patterns show marked differences between normal and psoriatic skin [12]. The overall approach in this work has been to examine the patterns of binding sites as far as possible by solvent extraction and enzyme digestion. In general, chloroform/methanol extraction has been used to identify features of the staining pattern not attributable to glycolipids [23] and Triton X-100 extraction to identify cytoskeletal constituents [24]. The purpose of neuraminidase and trypsin digestion has been to identify sites occluded by sialic acid [11] and protein, respectively.

MATERIALS AND METHODS

UEA I-FITC was obtained from Vector Laboratories, Burlingame, California. HPA was purchased from Pharmacia, Uppsala, Sweden or from Sigma Chemical Co., St. Louis, Missouri, and was fluoresceinated by the method of Rinderknecht [25]. Unreacted FITC was removed by chromatography on Sephadex G-25. The molar ratio of fluorescein to protein was 5.8. Trypsin (0.25%) was bought from GIBCO, Grand Island, New York. Neuraminidase, hyaluronidase, chondroitinase AC and ABC were obtained from Sigma Chemical Co. Skin samples were obtained from the Department of Dermatology, Stanford University Medical Center. Normal skin was generally obtained from meloplasty and psoriatic skin from 4-mm punch biopsies taken, with informed consent, under Xylocaine local anesthesia. Samples were embedded in OCT (Lab-Tek Products, Naperville, Illinois), frozen and stored at −70°C until required. Sections were cut at 4–8 μm using a Lipshaw cryomicrotome, air-dried, and stored at −70°C. Lectin binding was unaffected by storage for up to a year. Nine normal, 7 psoriatic plaque, and 5 psoriatic uninvolved specimens were used for the preparation of sections.

Reported values of the molecular weight of UEA I range from 170,000 [6], 45,000 [16] to two subunits of 31,000 and 32,000 on sodium dodecyl sulfate (SDS) gels (J. S. Whitehead, personal communication). For comparison of the results obtained here with other work, it was important to establish the value used in these studies. The molecular weights of the lectin conjugates were determined by chromatography on Sephadex G-75, Sepharose 4B, and Sephacryl S-300 using bovine serum albumin, ovalbumin, carbonic anhydrase, and soybean trypsin inhibitor as standards. The molecular weight of UEA I was found to be 63,000, i.e., a dimer of the 31,000 and 32,000 species observed on SDS gels. No association or dissociation was seen under the conditions of these experiments. HPA-FITC gave a single boundary on Sephacryl S-300 when chromatographed in the presence of 25 mM N-acetyl galactosamine. A molecular weight of 78,000 has been used in these studies [26].

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Abbreviations:
-FITC: designates the fluorescein conjugate
HPA: *Helix pomatia* agglutinin
PBS: phosphate-buffered saline
SDS: sodium dodecyl sulfate
UEA: *Ulex europeus* agglutinin

Staining

Slides were fixed in cold acetone for 5 min and air-dried. In experiments where sections were pretreated with neuraminidase (0.1 U/ml), chondroitinase (30 mU/ml), or hyaluronidase (30 U/ml), slides were flooded with enzyme in phosphate-buffered saline (PBS) and incubated for 30 min at 37°C. In some experiments, sections were extracted for 30 min with 1% Triton X-100 or with chloroform:methanol (1:1). Digestion with 0.025% trypsin in PBS was continued for 4 min at 23°C in the case of psoriatic material or 5 min at 37°C for normal. These were the maximal times for which the sections could be retained on the slide. All treated slides were washed twice with PBS for 15 min before staining. Slides were stained by flooding them with various concentrations of UEA I-FITC or HPA-FITC, incubating for 30 min at room temperature, washing for 15 min with PBS, and mounting in 22 mM citric acid, 58 mM Na_2HPO_4 in 50% glycerol/water. In later experiments, the mounting fluid of Huff, Weston, and Wanda [27], containing 10 μg/ml *p*-phenylene diamine in PBS:glycerol (1:9) was used. In control experiments, competing sugars were added: 0.5 M L-fucose for UEA I and 0.05 M N-acetyl-D-galactosamine for HPA.

Slides were examined using a Zeiss WL epi-illuminated fluorescence microscope with excitation illumination selected by a 450–490 nm bandpass filter and an FT 510 dichromatic beam splitter. Sections were examined through a 520–560 nm bandpass barrier filter. Objectives were Neofluars with numerical apertures of 1.3 (40×) and 0.8 (16×) and the photographic eyepiece was a 10× Wild Ultraphot. Under standard conditions, photographs were taken with the 40× objective, using a 2-min exposure on Kodak Tri-X film which was developed to 400 ASA. For comparison of staining patterns under different conditions, the image on photographic negatives was quantitated by microdensitometry. Comparisons were made between sections of the same skin sample, measured on the same day under the same conditions. Microdensitometry was carried out on negatives magnified 275× from the original section using a Joyce-Loebl Mark IIIC microdensitometer, with a slit opening of 250 μm and a 0–2.4 absorbance optical wedge. The method was calibrated using a flow cell with a diameter of 170 μm filled with suitable concentrations of UEA I-FITC and it was shown that, under the standard photographic conditions, the pen deflection was linear with UEA I-FITC concentration over the optical density range 0.06–1.1. In the case of normal skin, readings in corresponding regions (stratum granulosum, stratum spinosum, etc.) in sections treated in different ways were compared, but in psoriatic skin, where rather homogeneous staining occurred over considerable areas, readings were taken along transects at intervals equivalent to 7.3 μm on the original section.

RESULTS

Distribution of UEA 1 Binding Sites in Normal Epidermis

The staining pattern of UEA I-FITC on normal adult human epidermis depended on the concentration of the lectin, reflecting binding sites with a range of association constants. We distinguished two major patterns, one that occurred at low concentrations (≤ 0.26 μM) and the second at high concentrations (>0.26 μM–47 μM). At low concentrations, in agreement with Nemanic and Elias [7], Brabec et al [8], and Kariniemi et al [12], the most intense staining occurred on the membranes of cells at the boundary of the spinous and granular layers. Staining was essentially absent in the basal layer and of low intensity in the lower regions of the spinous layer. The concentration of binding sites increased rapidly in the more superficial cells of the spinous layer and then dropped sharply toward the stratum corneum. In sections in which washing was omitted, staining of this type could be detected at concentrations down to 8 nM. Omission of washing steps avoided problems arising from the very high rate of dissociation of the complex between UEA I-FITC and its binding site, which we found to have a half-life of 15 min (unpublished results). At high concentrations, cytoplasmic staining in the spinous layer became evident and increased up to the highest concentration of lectin used (Fig 1*B*). We have observed a wide range of intensity of staining of tissue from different normal individuals: in the course of this and other investigations, we have found 2 out of 25 nonpsoriatic specimens in which UEA I binding was barely detectable. We

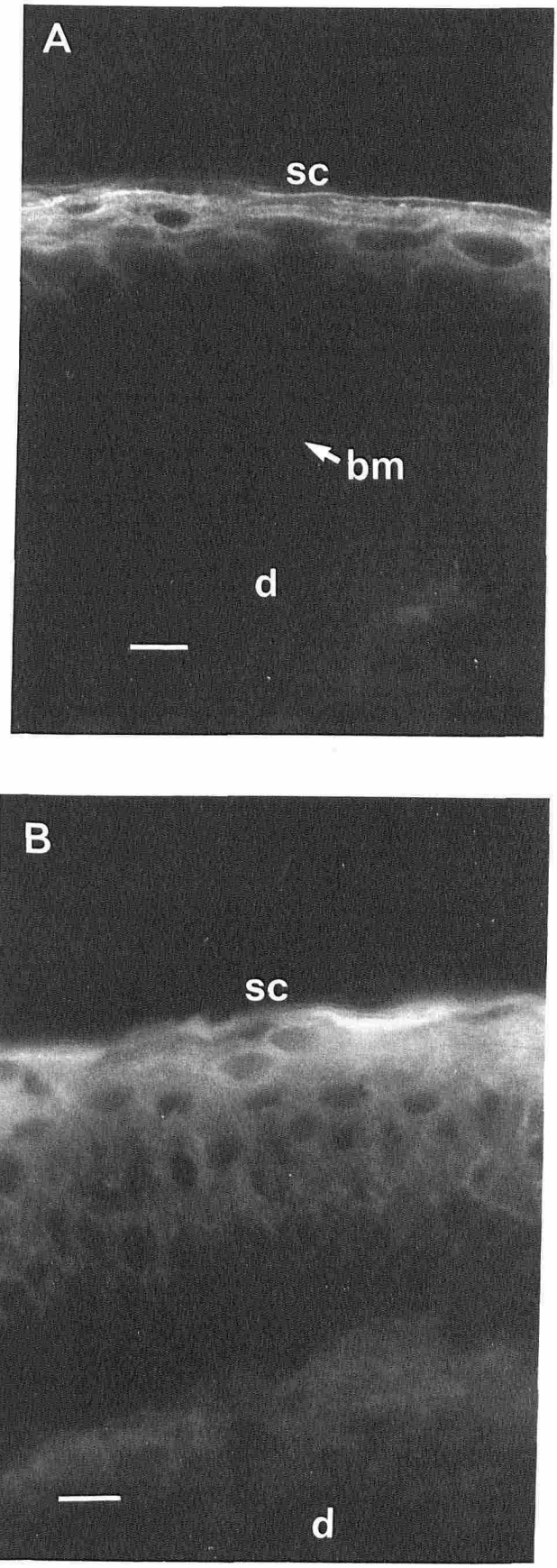


FIG 1. Binding of UEA I-FITC to normal skin. Unfixed sections of normal skin, cut at 4 μm, were stained with UEA I-FITC at 0.26 μM (*A*) or 4.7 μM (*B*) in PBS. Symbols: *d*, dermis; *bm*, basement membrane; *sc*, stratum corneum. *Bar* = 10 μm.

assume that these cases represent low values in a continuous distribution and are not exceptional.

Staining with UEA I-FITC was sensitive to blocking with 0.5 M L-fucose, as expected from the specificity of the lectin. Control experiments with unfixed sections showed that the intensity of fluorescence was variably reduced by up to 40% by extraction with acetone but showed no further change on chloroform/methanol extractions at either low or high lectin concentrations (Table I). The staining pattern was resistant to extraction with Triton X-100 and was unaffected by trypsin up to the point at which the section was lost from the slide. On digestion with neuraminidase, the bandlike pattern was unaffected. From these results, it was concluded that a major UEA binding site was a nonlipid component of the structural elements of the membrane, a conclusion which was supported by the demonstration that UEA I-FITC stained 1% SDS/1% mercaptoethanol-extracted keratinocyte envelopes.

Staining of Psoriatic Skin with UEA I-FITC

The pattern of staining in sections of psoriatic plaque epidermis at a concentration of 0.26 μM UEA I-FITC is shown in Fig 2. The band of membrane staining in the more superficial layers of the noncornified epidermis, seen in normal skin, was absent. Instead, the staining was found in the cytoplasm of cells above the basal layers, extending in some regions into the stratum corneum. The intensity of staining was generally low and varied from biopsy to biopsy, frequently showing a patchy distribution within a single section suggesting the irregularities in psoriatic severity that can be seen in hematoxylin and eosin-stained sections [28]. Broadly, cytoplasmic staining extending into the stratum corneum was most readily observed in regions showing extensive parakeratosis. Occasionally in areas of plaques showing no parakeratosis and the presence of a granular layer, slight membrane staining of the type seen in normal skin reappeared just below the horny layer.

Acetone fixation reduced the intensity of staining by 60% and subsequent extraction with chloroform/methanol removed all but 3% of the original fluorescence (Table I). The acetone-resistant staining was unaffected by Triton X-100, trypsin, and neuraminidase. In contrast to normal skin, the binding sites in psoriatic plaque epidermis are thus very largely lipid in nature.

Staining of Normal Epidermis with HPA-FITC

A typical section of normal skin stained with HPA-FITC is illustrated in Fig 3*A*. As has been reported previously [11], HPA stains the basement membrane and membranes of cells in the spinous and granular layers. Staining was unaffected by acetone fixation. No binding of HPA-FITC to the stratum corneum was seen and the basal layer was spared unless the section was digested with neuraminidase [11]. Following neuraminidase treatment, the keratinocyte membranes were stained throughout the malpighian layers, including the basal layer which showed about a 2-fold increase in staining over controls (Table I). Staining was sensitive to blocking with 50 mM N-acetyl-D-galactosamine, was halved on extraction with chloroform/methanol, but was insensitive to incubation with hyaluronidase, chondroitinase ABC or AC; so, the intercellular N-acetyl-D-galactosamine-containing polysaccharides of the skin, such as dermatan sulfate, were not involved in HPA binding. Trypsin had no effect on staining in the spinous layer but caused a variable increase in intensity in the region of the stratum granulosum, in some cases up to 2-fold. This band of staining extended into the lower layers of the stratum corneum. The enhancement was chloroform/methanol-sensitive and is interpreted as glycolipid/protein complexes in this region. It

FIG 2. Psoriatic skin section stained with UEA I-FITC. Unfixed sections of normal skin were stained with 0.26 μM UEA I-FITC. Symbols as in Fig 1. *Bar* = 20 μm.

TABLE I. *Microdensitometric evaluation of the effects of extraction and digestion on lectin binding to normal and psoriatic skin*

Treatment	UEA I				HPA			
	Normal			Psoriatic	Normal			Psoriatic
	G	S	B		G	S	B	
Acetone-fixed	1.58 ± 0.29	0.44 ± 0.16	0.20 ± 0.07	0.26 ± 0.05	0.97 ± 0.07	0.64 ± 0.11	0.35 ± 0.03	0.35 ± 0.12
Unfixed	1.72 ± 0.11	0.65 ± 0.16	0.36 ± 0.07	0.64 ± 0.08	1.07 ± 0.05	0.72 ± 0.10	0.47 ± 0.02	0.45 ± 0.13
$CHCl_3/CH_3OH$ extracted	1.47 ± 0.11	0.67 ± 0.23	0.33 ± 0.2	0.02 ± 0.02	0.66 ± 0.09	0.24 ± 0.04	0.15 ± 0.02	0.19 ± 0.09
Triton extracted	1.44 ± 0.11	0.6 ± 0.17	0.28 ± 0.13	0.29 ± 0.13	0.99 ± 0.08	0.13 ± 0.03	0.09 ± 0.02	0.13 ± 0.08
Neuraminidase	1.46 ± 0.14	0.60 ± 0.12	0.38 ± 0.11	0.28 ± 0.07	1.00 ± 0.05	0.69 ± 0.10	0.65 ± 0.09	0.71 ± 0.09
Trypsin	1.27 ± 0.17	0.61 ± 0.13	0.38 ± 0.12	0.33 ± 0.15	1.01 ± 0.09	0.45 ± 0.15	0.23 ± 0.03	0.14 ± 0.11
PNI − triton					0.93 ± 0.07	0.65 ± 0.11	0.32 ± 0.04	
PNI + triton					0.92 ± 0.03	0.61 ± 0.15	0.13 ± 0.03	
PNII − triton					0.84 ± 0.13	0.43 ± 0.10	0.24 ± 0.04	
PNII + triton					0.68 ± 0.07	0.26 ± 0.10	0.15 ± 0.01	

Details of the technique are given under *Materials and Methods*. The units are O.D. and data is given ± SD. G = upper spinous and granular layers; S = lower and midspinous layers; B = basal layer. PNI and PNII were two biopsies from lesion-free regions of psoriatic patients.

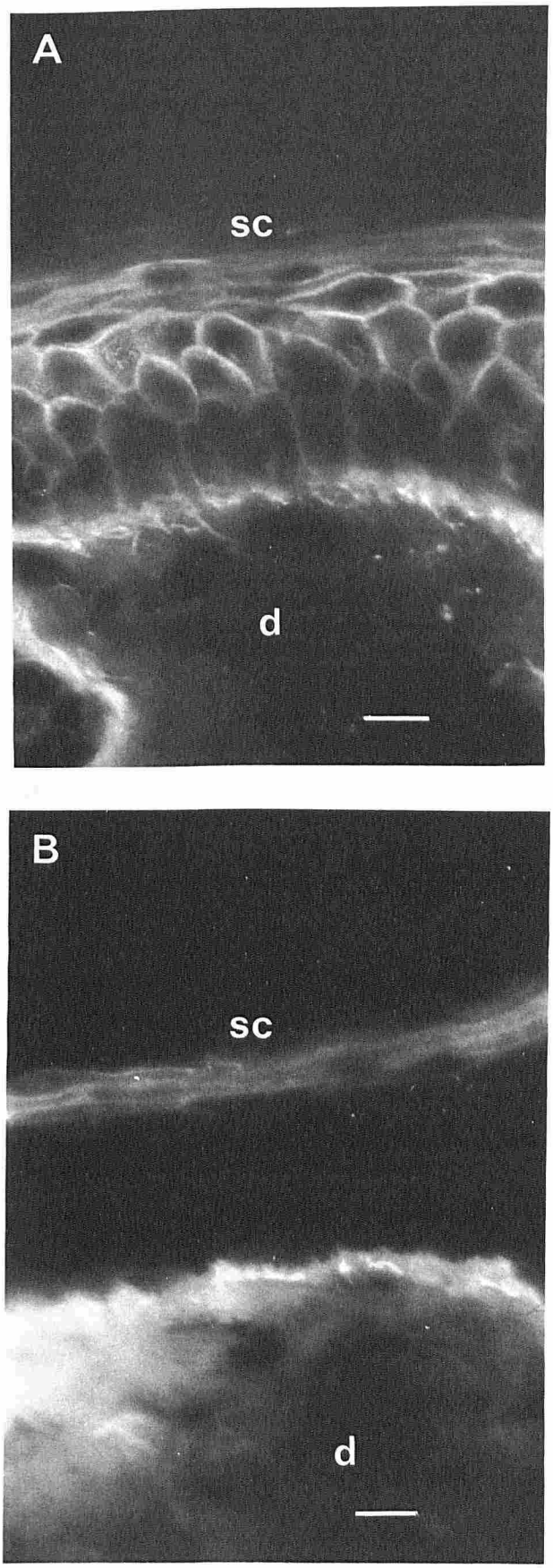


FIG 3. Effect of Triton X-100 on the staining of normal skin with HPA-FITC. Normal skin sections were stained with 128 nM HPA-FITC without (*A*) or following (*B*) extraction with 1% Triton X-100. Symbols as in Fig 1. *Bar* = 10 μm.

appeared that an HPA-binding glycolipid became increasingly covered by protein in the lower layers of the stratum corneum and was then destroyed. On extraction with Triton X-100, 90% of membrane staining in the spinous layer was lost although binding to the granular layer was largely unaffected (Fig 3*B*, Table I). Staining in the spinous layers thus appeared to be associated with nonstructural membrane components.

Staining of Psoriatic Epidermis with HPA-FITC

In psoriatic epidermis, staining with HPA-FITC was seen both in the cytoplasm and membranes of cells in the suprabasal regions and extended, in more severely affected areas, into the stratum corneum (Fig 4*A*). The basal layer was spared unless the section was digested with neuraminidase. As with UEA I-FITC, the intensity of staining varied considerably from biopsy to biopsy and from one region of a section to another. In general, cytoplasmic and membrane staining were unaffected by acetone fixation but both were reduced by chloroform/methanol extraction or trypsin treatment by a factor of about 2. Neuraminidase approximately doubled overall staining (Table I). In contrast to normal epidermis, Triton X-100 extraction of psoriatic skin left membrane staining unaffected in large areas. The results are illustrated in Figs 4*B* and 5. The microdensitometry trace (Fig 5) showed a reduction in the overall intensity of staining, largely as a result of loss of cytoplasmic lectin binding; but the amplitude of the peaks, caused by membrane staining, remained unaffected. This effect was observed in all specimens examined.

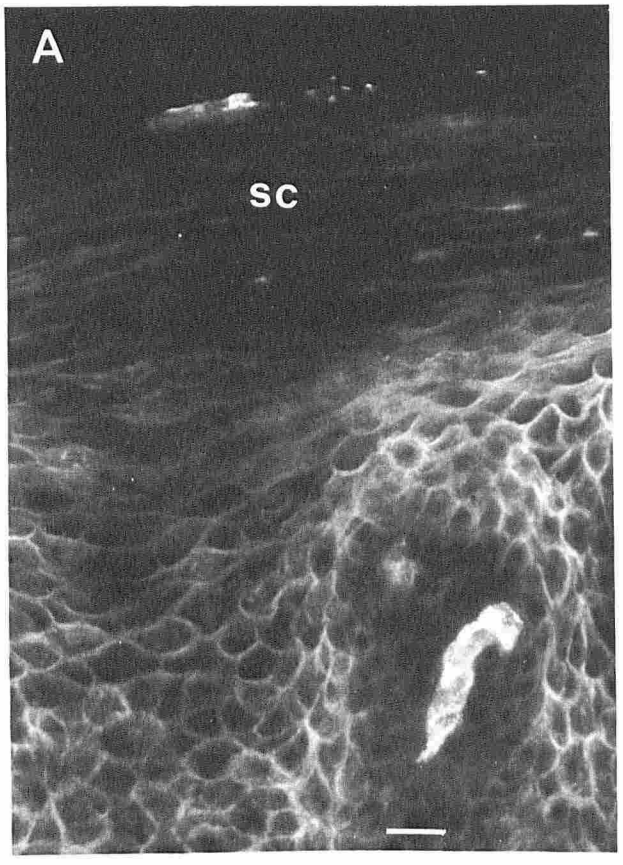
Staining of Clinically Uninvolved Epidermis from Psoriatic Patients with HPA

Epidermal biopsies from clinically uninvolved areas of psoriatic patients, when stained with HPA-FITC, appeared exactly as did normals. However, the sensitivity of HPA staining in the spinous layer to extraction with Triton X-100 varied considerably but was, in general, much less than normal epidermis, some specimens showing complete resistance (Table I). An example is illustrated in Fig 6.

DISCUSSION

The UEA I binding site of normal epidermal membranes is a late product of the maturation pathway, which, from its resistance to triton extraction appears to be a structural component of the cells. Moreover, its resistance to SDS/mercaptoethanol indicates that it is part of the mature keratinocyte envelope and this conclusion is supported by its trypsin resistance. Absence of such a component in psoriatic plaques is not surprising in view of the lack of a granular layer in psoriatic epidermis and is consistent with the observation of Buxman and Wuepper [29] of reduction of transglutaminase in active, parakeratotic regions of psoriatic plaques. The UEA I binding site seen in psoriatic skin is largely a trypsin-resistant, chloroform/methanol-soluble glycolipid, in contrast to the case in normal skin, and represents quite a different product. The finding of increased fucose-containing glycolipid is in accord with results of studies on the incorporation of fucose into glycoconjugates [18,19] and on changes in the binding of UEA I to dispersed keratinocytes in psoriasis [17]. The results support the view that major qualitative changes in oligosaccharide modification systems occur in psoriasis. Similar results have been reported by Kariniemi et al [12].

Binding of HPA to normal skin was of two types: triton-insensitive and triton-sensitive. The triton-insensitive site showed a distribution similar to UEA I and was largely a glycolipid. It was partially occluded by trypsin-sensitive protein, especially in the lower stratum corneum, and appeared to be a late maturation product. The triton-sensitive site was found in the spinous layer and appeared to be the major type of HPA binding site early in the normal maturation process. If



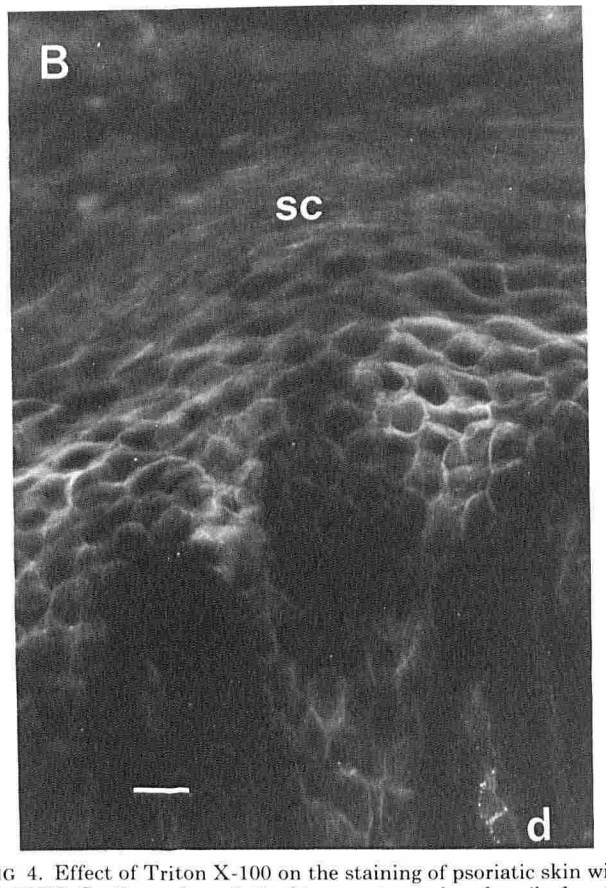


FIG 4. Effect of Triton X-100 on the staining of psoriatic skin with HPA-FITC. Sections of psoriatic skin were treated as described under Fig 3. *A*, Without extraction; *B*, following extraction with 1% Triton X-100 Symbols as in Fig 1. *Bar* = 20 μm.

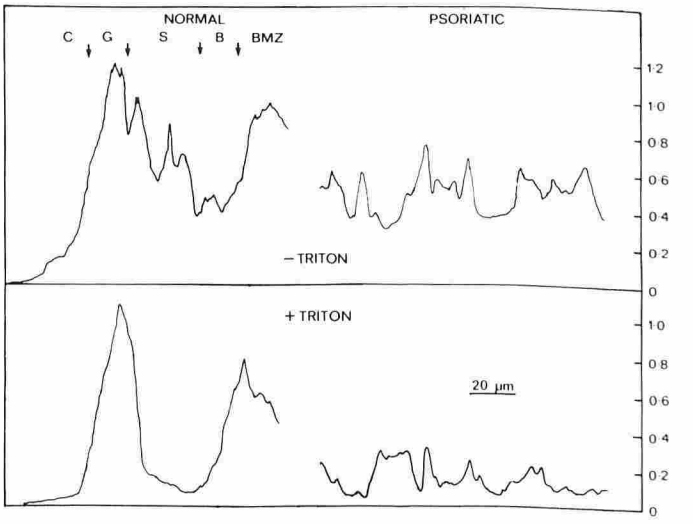


FIG 5. Effect of triton extraction on the intensity of HPA-FITC staining of normal and psoriatic skin. Microdensitometry scans of negatives of normal (*left*) or psoriatic (*right*) skin sections, without (*top*) or following (*bottom*) Triton X-100 extraction were obtained as described under *Materials and Methods*. The normal transects extend throughout the epidermis but the psoriatic traces are samples taken from the middle of the cellular epidermis, representing about 20% of an entire transect. *C* = stratum corneum; *G* = granular layer; *S* = spinous layer; *B* = basal layer; *BMZ* = basement membrane zone.

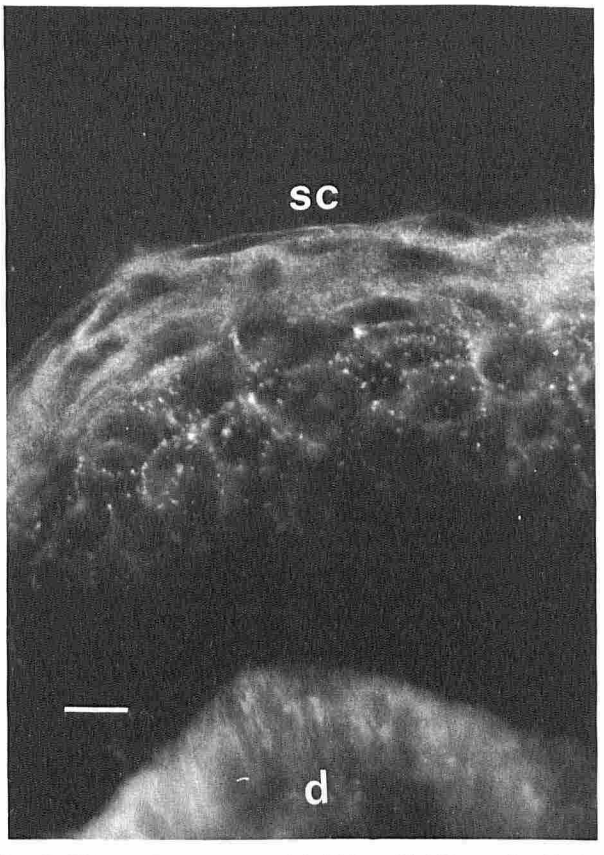


FIG 6. Effect of extraction with Triton X-100 on the binding of HPA-FITC to sections of uninvolved skin from a psoriatic patient. Sections of skin from an uninvolved region of a psoriatic patient were treated as described under Fig 3, with Triton X-100 extraction. Symbols as in Fig 1. *Bar* = 10 μm.

it is assumed that psoriatic keratinocytes are following the same maturation pathway as normal cells, albeit in a truncated manner, it would be expected that the triton-insensitive HPA binding site would be absent in psoriasis. This prediction is contrary to the experimental findings. In psoriasis, an HPA binding site is found associated with structural elements of the cell membrane early in the maturation process. The result provides evidence that the maturation pathway of keratinocytes in active psoriatic lesions differs qualitatively from that in normal skin and is not just abbreviated as a result of the rapid transit of the cells. This result is in accord with the loss of 67,000 dalton keratin [30–34], whose synthesis commences in the immediately suprabasal cells of the epidermis [35].

A further interesting feature of triton-resistance HPA staining is its appearance in the spinous layer of uninvolved skin of psoriatics. The amount is variable but we have found no difficulty in distinguishing specimens from normal and psoriatic individuals. The observation suggests the incipient expression of a cellular function which reaches full development in the psoriatic lesion and is consistent with the disease resulting from an alteration in the control of alternative pathways of maturation. A similar conclusion was drawn from studies on the induction of epidermal proliferation in the symptomless skin of psoriatics by propanalol injection or tape-stripping [36]. In the case of triton-resistant HPA binding, however, the observation is related to a marker for maturation and occurs without any stimulus. It suggests that even in clinically uninvolved skin of psoriatic patients, the keratinocytes are already showing some induction of the alternative pathway. The presence of this staining reaction may provide a marker for latent psoriasis and be more convenient than the estimation of labeling index after propanalol injection.

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